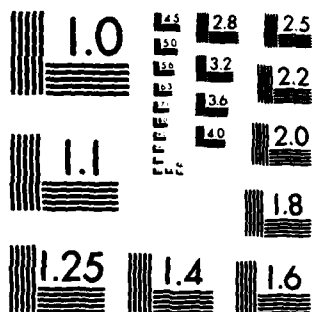END
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CARDIO-PULMONARY RESPONSE TO SHOCK

ANNUAL PROGRESS REPORT

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Pressure breathing and particularly end-expiratory pressure will induce the pulmonary production of prostaglandins (PG). These PGs regulate cardiac contractility and the release of plasmin mediated fibrinolytic activity. A high molecular weight protein has been tentatively identified as the circulating negative inotropic agent whose production is stimulated by PG synthesis during end-expiratory pressure. The large amount of prostacyclin (PGI_2) secreted by the lungs in response to surgery may protect against microaggregate entrapment and damage of the lungs. PGI_2 infusion is effective therapy for experimental

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pulmonary embolism.

CONTENTS

1. Prostaglandin Production in Response to Surgical Trauma (1)

This is a study of the role of surgery in causing secretion of the power-
ful antiaggregating and vasodilating prostaglandin (PG)I_2 and the possible
platelet and cardiovascular sequelae of this secretion. Radioimmunoassays
were used to measure the stable metabolites of PGI_2 (6-oxo-$PGF_{1\alpha}$) and thrombox-
ane A_2 (TxB_2).

Following barbiturate anesthesia and mechanical ventilation in 10 dogs,
PGI_2 levels rose from 0.023 ± 0.03 ng/ml ($\bar{x} \pm SE$) to 0.056 ± 0.001 ($p < .03$).
Laparotomy or thoracotomy was followed by a prompt rise in arterial PGI_2 levels
to 0.26 ± 0.04 ($p < .005$), higher than pulmonary arterial levels ($p < .05$).
Despite the increase in PGI_2, platelet counts fell by $21,000/mm^3$ ($p < .05$),
while mean arterial pressure (MAP) fell 20 mm Hg ($p < .03$) and cardiac output
increased 0.6 L/min ($p < .05$).

These results indicate that local surgical trauma can stimulate the
pulmonary secretion of PGI_2 to levels that have been reported to inhibit platelet
aggregation. These levels fail to prevent platelet consumption, presumably
by the surgical wound. The cardiovascular alterations, fall in MAP and rise
in flow are consistent with the known actions of PGI_2.

2. Pulmonary Regulatory Controls of Systemic Organ Function

a) Lung Metabolism and Systemic Organ Function (2)

In the past decade a variety of metabolic events have been described
which occur in the lungs. These processes such as the clearance of serotonin
and norepinephrine, the inactivation of bradykinin and the activation of
angiotensin II, and the synthesis of prostaglandins may have a direct impact
on systemic organ function. Under certain circumstances the lungs produce
prostaglandins that may lead to severe hemodynamic instability and death.
Pressure breathing with hyperinflation is a potent pulmonary metabolic stimulus.

This commonly used therapeutic maneuver has been shown to increase fibinolytic activity. The application of end-expiratory pressure will further enhance the fibrinolytic state by virtue of the pulmonary secretion of plasminogen activator. Positive end-expiratory pressure (PEEP) will also cause a lowering of the cardiac output, which is related at least in part to lung metabolism. Circulating factors are released during PEEP that have a negative inotropic effect. It is reasonable to view respiratory failure not only as a defect in gas exchange but also as a derangement in lung metabolism.

   b) Blood Flow and Its Distribution (3)

   Current evidence is inconclusive regarding the possibility that positive end-expiratory pressure (PEEP) redistributes flow and may be directly responsible for systemic organ dysfunction. This study tests the hypothesis that PEEP may induce abnormalities in the distribution of cardiac output (CO). Eight anesthetized dogs were studied during (1) 0 cm H_2O PEEP (Z_1); (2) 15 cm H_2O PEEP (P); (3) Z_2; and (4) bleeding (B) to reduce the CO to the same level as P. At each of the four periods, a different 15 μ radiolabelled microsphere was injected into the left atrium. Another four dogs were used to varify that each type of microsphere had the same flow distribution. CO fell from 3.1 liters/min to 1.9 during P (p < 0.01) and 2.0 during B (p < 0.01). Mean arterial pressure (MAP) declined from 102 to 83 mm Hg (p < 0.01) and 86 mm Hg (p < 0.01), respectively. Left atrial pressure (LAP) rose from 5.0 to 7.9 mm Hg during P (p < 0.01) and fell during B to 2.7 mm Hg. CO and its distribution were the same during Z_1 and Z_2. P caused selective reductions in hepatic (52%), adrenal (25%), and bronchial (24%) blood flows (p < 0.01). In contrast, total flow to these organs during B was the same as during Z. Total renal flow was unchanged by P or B, but the cortical:medullary flow ratio increased during P from 24 to 49 (p < 0.01) and was unchanged by B. P induced a decrease in

fundal mucosal flow as compared with Z (p < 0.01). Total coronary flow fell from 100 to 64 ml/min during both P and B (p < 0.01). P led to a selective fall in subendocardial flow (67 ml/min x 100 gm) as compared with B (82.5 ml/min x 100 gm, p < 0.01) as well as in the subendocardial:subepicardial flow ratio (1.069 vs 1.112 ml/min x 100 gm, p < 0.05). It is likely that the higher left ventricular filling pressure (LAP) during P as compared with during B compressed the endocardium and induced relative ischemia. Similarly the high airway pressure during P may have impeded bronchial mucosal flow. The causes and consequences of the other P-induced variations in flow are speculative.

c) Diminution in Cardiac Contractility (4)

Application of positive end-expiratory pressure (PEEP) will reduce cardiac output (CO). Humoral mediation of this event by circulating negative inotropic agents was examined using a rat papillary muscle bioassay. Twenty-seven dogs were anesthetized with an IV pentobarbital infusion. Plasma was obtained before and after 30 minutes of PEEP. The plasma was oxygenated in a small (4.5 ml) papillary muscle chamber using a diffusion membrane. An average PO_2 of 416 mm Hg was achieved. PEEP plasma reduced developed tension (Tpd) from 2.16 ± 1.0 to 1.90 ± 1.05 g (p < 0.001). A fall in Tpd was observed whether or not CO was maintained constant with fluid infusion. Resting tension was unchanged. The percent reduction in Tpd correlated with the fall in CO (r = 0.63, p < 0.01) when fluid was not infused to maintain CO. Reapplication of control plasma restored Tpd. Barbiturate levels in anesthetized dogs rose from 17.3 to 19.4 µg/ml during PEEP (p < 0.1). Addition of pentobarbital to normal plasma led to a slight decrease in Tpd only when the concentration exceeded 99 µg/ml during PEEP (p < 0.1). Addition of pentobarbital to normal plasma led to a slight decrease in Tpd only when the concentration exceeded

99 μg/ml. In three experiments on ex-vivo perfused hearts, application of PEEP led to lowering of peak systolic pressure (PSP) within 5 minutes. Removal of PEEP restored PSP in a similar time. The results support the hypothesis that the decline in CO with PEEP is mediated in part by a circulating negative inotropic agent.

d) Stimulation of Fibrinolytic Activity (5)

This study examines the role played by pressure breathing in stimulating the fibrinolytic system. Twenty-one anesthetized dogs were intubated. Euglobulin lysis times, expressed as FA units were obtained in ten dogs (Group I) from femoral (a), pulmonary artery (p), infra (i) and supra (s) renal vena caval blood. During spontaneous breathing FA activity increased across the peripheral circulation from FA_a = 3.2 ± 0.6 units (mean ± standard deviation) to FA_i = 4.5 ± 0.9 (p < .01) and further increased after admixture with renal blood, FA_s = 7.9 ± 0.6 (p < .001). Hepatic clearance reduced FA_p to 5.3 ± 1.1, but this level remained higher than FA_a (p < .01) indicating loss of FA in the lungs. Positive inspiratory pressure, $ZEEP_1$ (rate 12, tidal volume 15 ml/kg) increased FA_a to 5.8 ± 0.9 a value now higher than FA_p (p < .05). After application of end-expiratory pressure, (15 cm H_2O PEEP) FA_a rose to 8.5 ± 1.0, higher than $ZEEP_1$ (p < .001). FA_a returned to $ZEEP_1$ levels with removal of PEEP. During the study, FA_i increased with FA_a (r = .67, p < .05) while FA_p and FA_s remained constant. This indicates a reciprocal relationship between renal and pulmonary FA function. Lung biopsy showed a 13.3% fall in saline extractable plasminogen activator during ZEEP (p < .05) and a 37.9% fall after PEEP (p < .001). Fibrinogen, plasminogen and fibrin degradation products were unchanged. When lung biopsy was omitted in eleven dogs (Group II) the response to pressure breathing was similar to Group I. FA measured as ng fibrin lysed, remained higher in arterial compared to pulmonary arterial blood (p < .001). PEEP accentuated this difference

(p < .001). These results indicate that the lungs normally extract and perhaps store plasminogen activator, secreted in large part by the kidneys. Pressure breathing, particularly PEEP, causes the release of activator from the lungs with an increase in arterial and peripheral venous FA activity.

3. Endothelial Functions

　　a) Control of Plasminogen Activator Secretion (6)

Bovine aortic endothelial cells (EC) in culture during their log phase of growth secrete plasminogen activator. Hydrocortisone, dibutyryl cAMP, theophylline, colchicine and cycloheximide, dependent upon concentration, inhibit plasminogen activator activity. Several substances associated with inflammation and thrombosis, such as thrombin, serotonin, catecholamines, histamine, vasopressin, endotoxin and indomethacin, at the concentrations tested, did not significantly alter plasminogen activator activity when compared with controls.

　　b) The Role of Serotonin in Protecting Against Capillary Fragility (7)

The effect of serotonin on vascular fragility, visible as petechiae, was examined in antiplatelet serum-induced thrombocytopenic hamsters. Serotonin was administered intravenously or intraperitoneally, and following a single injection of 0.5 mg/100 gram body weight, a temporary inhibition of petechial formation for approximately one hour was observed. Repeated serotonin injections maintained animals free of petechiae for the four hour period of administration. Plasma levels of serotonin and the effect of serotonin on cutaneous perfusion were not significant factors in the observed inhibition of petechiae. The data suggest that in normal animals platelet serotonin may contribute more than platelet adhesion to maintain microvascular integrity.

c) Serotonin Clearance By Capillaries (8)

We have demonstrated directly that capillary EC have serotonin (5-HT)
receptors. In contrast to intimal EC, 5-HT uptake is affected by MAO in-
hibition with iproniazid and appears to be unaffected by 5-HT analogs.

4. Role of Prostaglandins

a) Decrease in Contractility (9)

Positive end-expiratory pressure (PEEP) is known to reduce cardiac
output (CO) and alter the pulmonary metabolism of vasoactive agents. This
study isolates the mechanical from the pulmonary metabolic changes induced
by PEEP and examines the influence of the latter on hemodynamics.

Experiments were conducted in 25 isolated, temperature controlled,
ventilated canine left lower lobes (LLL), undergoing perfusion from a
support dog at a fixed flow of 300 ml/min. In Group I (10), an isolated
paced, isovolumetrically contracting dog heart undergoing retrograde
coronary perfusion was placed in circuit between the LLL and the dog. A
left ventricular balloon was used to construct Starling curves. Application
of 15 cm H_2O PEEP to the LLL led to a fall in peak systolic pressure (PSP)
at each of 5 diastolic pressures (DP) tested in the range of 18 to 30 mm Hg
($p < .05$ to $.005$). Thus, at a DP of 23 mm Hg PSP fell from 136 ± 26 (mean $\pm$ SD)
to 120 ± 27 mm Hg ($p < .005$). In Group II (6) and III (9) the heart was ex-
cluded. Support animals and LLL donors of Group III were pretreated with
indomethacin 5 mg/kg IV. PEEP applied to the LLL of Group I and II led to
a fall in support dog CO from $2.79 \pm .92$ to $2.24 \pm .81$ L/min ($p < .02$) and
mean arterial pressure (MAP) from 113 ± 17 to 100 ± 26 mm Hg ($p < .01$).
PEEP yielded no change in CO or MAP in Group III. Pulse, pulmonary arterial
wedge pressure (PAWP), blood gases and pH remained constant in all groups.
With the LLL excluded, the pump perfusion circuit itself did not influence
support dog hemodynamics.

The results strongly suggest that PEEP stimulates the lungs to produce prostaglandins which reduce contractility and alter vasoactivity.

Separation procedures and assay of various molecular weight fractions using myofibril ATPase activity has tentatively identified the negative ino-tropic agent as a high molecular protein of approximately 125,000. This protein is found during 15 cm H_2O positive end-expiratory pressure, but not during 0 cm H_2O PEEP.

b) Control of Plasmin-Mediated Fibrinolytic Activity (10)

The lungs are thought to regulate circulating fibrinolytic activity (FA). Pressure breathing or hyperventilation stimulates the metabolic activity of the lungs and causes the secretion of both FA as well as prostaglandins. The interrelation between these events is the subject of the present study.

Thirteen dogs were anesthetized, intubated, ventilated and subjected to 0 cm H_2O end-expiratory pressure (0-EEP) or 15 cm H_2O PEEP. After 30 minutes pulmonary and systemic arterial blood was drawn. One set of euglobulin fractions was prepared for the measure of total FA while the other was pre-pared from plasma from which all plasminogen and plasmin had been removed by affinity chromatography. This FA is non-plasmin dependent. The plasmin dependent FA is obtained by subtracting non-plasmin activity from total FA. All FA is expressed as ng fibrin lysed.

During 0-EEP the lungs secreted FA. Total FA in arterial blood was 145 ± 15 (mean ± SE). This was higher than pulmonary arterial (PA) blood, 87 ± 9 (p < .01). PEEP increased pulmonary secretion such that arterial levels rose to 238 ± 15 (p < .01) while PA levels rose modestly to 113 ± 9. In-creases in plasmin mediated FA accounted for these changes during PEEP; arterial levels were 180 ± 13 and PA values were 76 ± 12 (p < .001). There were no changes in non-plasmin mediated FA. After indomethacin, 5 mg/kg IV,

plasmin mediated activity was almost completely abolished (p < .001). Arterial levels fell from 90 ± 3 to 3 ± 2, and PA levels fell from 45 ± 6 to 7 ± 3. Further, pulmonary FA production was unchanged by PEEP.

These results indicate that pressure breathing and particularly PEEP will stimulate the secretion of plasmin mediated FA. This event is mediated by a prostaglandin.

5. Prostacyclin in the Therapy of Pulmonary Embolism (11)

In theory, PGI_2 should be useful for the therapy of pulmonary embolism because of its ability to inhibit platelet aggregation, dilate the pulmonary vasculature and stimulate fibrinolytic activity. This hypothesis was tested in 12 dogs who were given autologous blood clot, 0.5 g/kg IV labeled with I-125 fibrin.

One hour following embolization, mean pulmonary arterial pressure (MPAP) had risen 13 mm Hg above the baseline value of 19 ± 3 mm Hg (mean ± SD), (p < .005). Pulmonary vascular resistance was also elevated (p < .001). The physiologic shunt ($\dot{Q}_S/\dot{Q}_T$) rose to 24 ± 8% from a baseline value of 15 ± 6% (p < .001). Six dogs were given PGI_2 100 ng/kg·min IV for one hour. This reduced mean arterial pressure (MAP) by 27 mm Hg (p < .001) and MPAP by 3.8 mm Hg (p < .02). $\dot{Q}_S/\dot{Q}_T$ decreased (p < .001) and fibrin degradation products appeared, 18 ± 8 µg/ml compared with 7 ± 3 µg/ml in untreated dogs (p < .05). A diuresis was noted and increased I-125 activity was found in the urine of PGI_2 treated animals (p < .04). After the PGI_2 infusion was stopped, MAP rose promptly. $\dot{Q}_S/\dot{Q}_T$ continued to improve and was similar to baseline values within another hour. Control animals remained significantly hypoxic compared to the treated group (p < .005). Cardiac output declined immediately after PGI_2 was stopped, and after two hours had fallen by 0.81 L/min (p < .001). This was similar to the depressed flow value seen in untreated animals.

The results demonstrate that the antiaggregating agent PGI_2 promptly reverses the physiolgic shunting associated with pulmonary embolism. Other salutary effects relate to enhanced fibrinolysis and maintenance of cardiac output.

6. Technical Improvements

    a) Papillary Muscle Test Chamber (12)

    A system to measure contractility of a rat papillary muscle is described. It is unique in that the unit requires less than 5 ml plasma as the bathing medium. A membrane oxygenator built into the muscle chamber permits the development of stable oxygen tensions of over 500 mm Hg and the elimination of plasma foaming.

    b) Water Jacketed Syringe

    A simple water cooled syringe system has been developed and used in animal experiments. The purpose is to preserve the unstable compound PGI_2 during infusion by maintaining its temperature at $4^{\circ}C$. Modification of the pH to a range of 9 to 10 is also of utmost importance. This system maintains biologic activity of the PGI_2 for over one day.

7. Oxygen Transport (13)

    One or more of the several components of the oxygen transport system may function abnormally in critical illness. Arterial hypoxemia is an important feature of acute respiratory failure. Its prominence may obscure other limitations in oxygen availability such as low cardiac output, anemia or an increased red cell affinity state. These several components of the oxygen transport system can be influenced by therapeutic maneuvers, but the result may not necessarily be a net benefit. For example, red blood cell transfusion therapy may correct anemia, but increase the red blood cell affinity state so as to adversely affect cardiac function. Treatment programs require consideration of the interaction of these several variables affecting oxygen transport.

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